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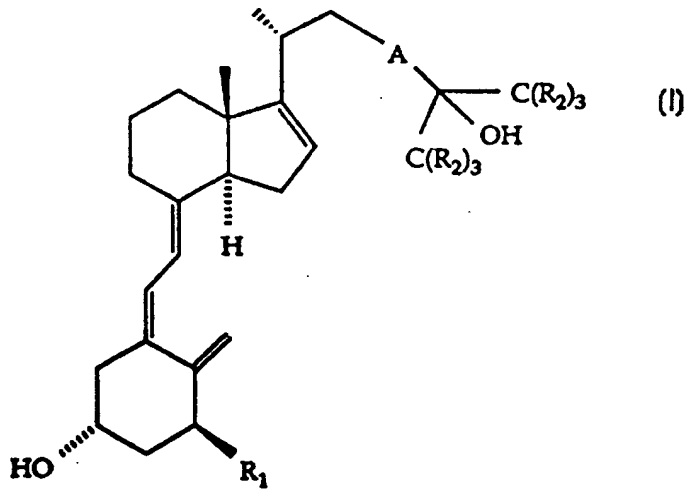
(54) Title: COMPOSITIONS CONTAINING VITAMIN D DERIVATIVES FOR TREATMENT OF PHOTODAMAGED SKIN

(57) Abstract

Compositions containing compounds of formula (I) wherein R_1 is hydrogen, hydroxy or fluorine, R_2 is hydrogen or halogen and A is (a), (b) or (c), provided that when A is $-CH_2-CH_2-$, R_2 is hydrogen; for topical agents to combat disorders of the skin produced by photodamage such as wrinkling, elastosis and premature aging.



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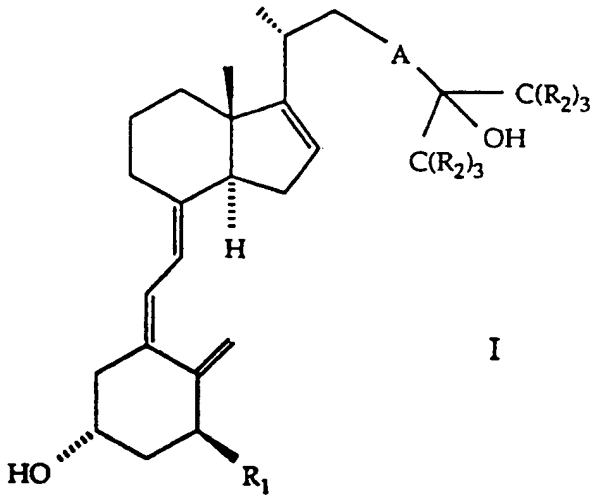
COMPOSITIONS CONTAINING VITAMIN D DERIVATIVES FOR TREATMENT OF PHOTODAMAGED SKIN

The skin, particularly in humans, contains an elaborate network of elastin fibers which are responsible for maintaining its elastic properties. With excessive exposure to sunlight the elastic fiber system becomes hyperplastic, disorganized and ultimately disrupted. This is known as actinic elastosis and is the principal cause of wrinkling, discoloration and laxity of the skin in the exposed areas of the body. The skin can repair itself to some extent but it is nevertheless desirable to have an agent which can accelerate the repair of this prematurely aged skin.

This invention relates to compositions for the treatment of photodamaged skin.

More particularly this invention relates to compositions for topically treating conditions associated with photodamaged skin containing a compound of the formula



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wherein R_1 is hydrogen, hydroxy or fluorine, R_2 is hydrogen or halogen and A is $-C\equiv C-$, $-C=C-$ or $-CH_2-CH_2-$, provided that when A is $-CH_2-CH_2-$, R_2 is hydrogen.

This invention also relates to the use of a compound of formula I for the manufacture of a composition for the topical treatment of conditions associated with sundamaged skin.

The term "lower alkyl" as used herein denotes groups which preferably contain 1-4 carbon atoms. Alkyl groups can be straight-chain or branched-chain, such as, for example, methyl, ethyl, propyl, butyl, isopropyl and the like. Preferred lower-alkyl groups are methyl or ethyl. The term "halogen" embraces fluorine, chlorine, bromine and iodine, of which fluorine is preferred.

Of the compounds of formula I, there are preferred compounds wherein R_1 is fluorine or hydrogen. Further, preferred compounds of formula I are those in which R_2 is fluorine or hydrogen and A is a double bond or triple bond. Particularly preferred are compounds of formula I wherein R_1 is hydrogen , R_2 is fluorine, and A is a double bond.

The following compounds of formula I are especially preferred:

1α-fluoro-25-hydroxy,16-ene-23-yne-26,27-hexafluoro-cholecalciferol;

1α-fluoro-25-hydroxy,16,23E-diene-26,27-hexafluoro-cholecalciferol; and

25-hydroxy-16,23E-diene-26,27-hexafluorocholecalciferol.

Processes for preparing compounds of formula I, wherein A is $-C\equiv C-$, $-C=C-$ or $-CH_2-CH_2-$, R_1 is hydrogen or hydroxy and R_2 is hydrogen are set forth in U.S. Patent No. 5,087,619.

Processes for preparing compounds of formula I, wherein A is $-C=C-$, R_1 is hydrogen, hydroxy or fluorine and R_2 is fluorine are set forth in U.S. Patent No. 5,428,029 .

Processes for preparing compounds of formula I, wherein A is $-C\equiv C-$, R_1 is fluorine, hydrogen or hydroxy and R2 is halogen are set forth in U.S. Patent 5,451,574.

The compounds of formula I when applied topically to the skin, reverse the condition associated with photodamage so as to moderate and retard the damage to the skin caused by sun exposure. The damage caused sun exposure may include premature aging, elastosis and wrinkling. This damage is more pronounced in older patients. By applying the compounds of formula I topically to the skin in an amount effective to reverse the conditions associated with photodamage, the acceleration of skin repair is accomplished to enhance the skin with a smoother and younger appearance. The compounds of formula I should be applied to that portion or area of the skin which is affected by photodamage or in which treatment is desired. The use of the compounds of formula I in accordance with this invention can provide the effects of anti-aging and anti-wrinkling, as well as enhance the repair of sun damaged skin.

A compound of formula I, or a combination of compounds of formula I can be applied in accordance with this invention to human skin in conventional topical compositions. These compositions can be utilized to apply compounds of formula I to the skin of the body, particularly the face, legs, arms and hands. The preferred method of application of compounds of formula I topically to produce the best effects should start where a patient is between 30 and 55 years of age, when elastosis begins to appear and becomes more pronounced. Thereafter, this composition can be continuously applied to patients to reduce the effects and injury associated with sun exposure. Generally, it is preferred to begin the treatment when the patient reaches approximately 30 years of age and to continue the treatment throughout his life, in order that the effects of elastosis be reduced and to prevent any further progression of photodamage.

The compounds of formula I can be administered in accordance with this invention in any conventional suitable topical preparation, that is, in combination with any suitable conventional carrier useful for topical administration. Therefore, compounds of formula I can be administered in accordance with this invention in any suitable topical composition such as a cream, ointment, soap, solution, lotion, emulsion, shampoo, and the like. Generally, for most efficacious results, these topical compositions contain from about .00001% to about .1% by weight of the total composition of a compound of formula I, with amounts of from about .0001% to about .01% by weight of the composition being especially preferred. If desired, higher concentrations may be utilized depending upon the nature and extent of elastosis.

In formulating these compositions, any conventional non-toxic, dermatologically acceptable base or carrier in which a compound of formula I is stable can be utilized. The preferred compositions for use in this invention are the conventionally cosmetic compositions which can contain a cosmetically active ingredient which is topically administered to human skin to provide a cosmetic effect. Among the conventional cosmetically active materials which can be utilized in this composition are included: sunscreens, penetration enhancers, moisturizers, surfactants, emollient, colorants, conditioners, bacteriocides, astringents, detergents, and the like. The topical compositions of this invention can, if desired, contain suitable sunscreen agents. Any conventional sunscreen agent can be utilized in formulating the formulations containing compounds of formula I which can be utilized in accordance with this invention.

These topical compositions which contain compounds of formula I can contain any of the conventional excipients and additives commonly used in preparing topical compositions. Among the conventional additives or excipients, which can be utilized in preparing these cosmetic compositions in accordance with this invention are preservatives, thickeners, perfumes and the like. In addition, the conventional antioxidants, such as

butylated hydroxyanisoles (BHA), ascorbyl palmitate, propyl gallate, citric acid, butylated hydroxy toluene (BHT), ethoxyquin, tocopherol, and the like can be incorporated into these compositions. These topical compositions can contain conventional acceptable carriers for topical applications which are generally utilized in these compositions. These compositions may contain thickening agents, humectants, emulsifying agents and viscosity stabilizers, such as those generally utilized. In addition, these compositions can contain flavoring agents, colorants, and perfume which are conventional in preparing cosmetic compositions.

The topical compositions containing compounds of formula I can be applied to the skin and should be preferably applied once daily to the skin. For obtaining the reversal of the elastosis so as to impart to the skin a smooth and younger appearance, the topical compositions should be preferably applied for a period of 6 months. After that, compositions which contain compounds of formula I should be applied continually to maintain the effect of younger and smoother skin. These preparations can be applied according to the need of the patient as determined by the prescribing physician. In any event, the particular regimen for application of this composition to a patient will typically depend on the age, weight and skin condition of the individual.

The UVB irradiated hairless mouse has been found to be a convenient model for actinic elastosis in the skin. (Kligman et al. J. Invest. Dermatol. 78:181 (1982). It has been shown by Johnston et al. in J. Invest. Dermatol. 82:587 (1984) that irradiation with low levels of UVB which simulate realistic solar exposure leads to a significant increase in skin elastin as measured by desmosine content. The amount of this amino acid, which is isolated from acid hydrolysis of elastin, is proportional to the elastin present in the skin. (Uitto et al., Lab. Invest. 49:1216 (1973). Treatment of irradiated mice with topical retinoic acid has been shown to normalize the histological features of the skin in which the previously elastoic dermis has the appearance of

unirradiated tissue (Kligman et al., Conn. Tissue Res. 12:139 (1984), Kligman U.S. Patent No. 4,603,146 July 1986). Therefore, this model can be used to determine the efficacy of compounds in the repair of sun damaged skin.

Repair of UVB-Induced Dermal Damage in the Hairless Mouse by Compounds of Formula I

Hairless mice (female, HRS/J strain, Jackson Labs, 5-7 weeks old at the start of the experiments) were housed in yellow light and irradiated three times per week with a bank of 8 Westinghouse Sunlamps (FS72T12 HO, peak irradiance at 313 nm) placed about 20 cm above the animals. UVB output was measured on an International Light Research Radiometer, model IL 1700, using a SEE240 detector. With this setup, the lamp output was approximately 3.5 mW/cm^2 and the time of exposure for 0.06 J/cm^2 was about 17 seconds; 1 MED is approximately 0.03 J/cm^2. The precise dose was delivered by a IL 844A Phototherapy Exposure Control. Daily doses were 0.03 J/cm^2 for two weeks, 0.06 J/cm^2 for two weeks and 0.08 J/cm^2 thereafter, until a total dose of approximately 4 J/cm^2 was accumulated. To effect repair of the dermal damage, the UVB irradiation was discontinued and the animals were divided into groups of approximately eight and treated three times per week with various concentrations of the vitamin D analogs dissolved in ethanol. All dosing was done under yellow light.

A control group treated with acetone alone was included. Two-cm strips of dorsal skin were taken longitudinally down the center of the irradiated (and treated) area. Elastin fibers were stained with Luna's aldehyde fuchsin and collagen by Van Gieson. In this model, repair is defined by the appearance of a normalized dermis extending from the epidermis down to the layer of compressed elastin. The extent of repair is reflected by the width of this zone. In these studies, since the width of the

zone varies considerably, the area of the zone on a standard length of histological section is measured by image analysis. Compounds are tested at three doses and an approximate ED_{50} calculated.

The results are given in Table I.

TABLE I

Compound	Dose (μg)	Repair Zone mm^2
Group A		
Control		0.003±0.002
Compound A	0.5	0.484±0.192*
	0.05	0.113±0.054
Compound B	5.0	0.922±0.149***
	0.5	0.485±0.105**
Group B		
Control		0.035±0.009
Compound B	10.0	0.331±0.091*
	2.0	0.303±0.082*
Group C		
Control		0.0028±0.0008
Compound B	2.0	0.0534±0.0086***
Compound C	0.1	0.0088±0.0111
	0.5	0.0200±0.0106**

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs vehicle control

Throughout the specification, Compound A is 1α-fluoro,25-hydroxy-16-ene-23-yne-26,27-hexafluorocholecalciferol;

Compound B is 25-hydroxy-16,23E-diene-26,27-hexafluorocholecalciferol;

Compound C is 1α-fluoro,25-hydroxy-16,23E-diene-26,27-hexafluorocholecalciferol;

The invention is further illustrated in the following examples. These examples are for illustration and are not limitive of the claimed invention.

Creams, gels and solutions containing ingredients within the proportions set forth in Examples 1 through 3 below, can be formulated by conventional means. Reference to Compound A in the Examples is illustrative of any of the claimed compounds.

Example 1

Cream

Ingredients	% w/w
Compound A	0.00001 - 0.10
Cetyl Alcohol	1.50
Stearyl Alcohol	2.50
Sorbitan Monostearate (Span 60)	2.00
Mineral Oil	2.00
Glyceryl Monostearate and Polyoxy-ethylene Glycol Stearate Blend (Arlacel 165)	4.00
Polysorbate 60 (Tween 60)	1.00
Caprylic/Capric Triglyceride	5.00
Sorbitol Solution	4.00
Edetate Disodium	0.10
Butylated Hydroxyanisole (BHA)	0.02
Sorbic Acid	0.20
Potassium Sorbate	0.1 - 0.2
Water q.s. to	100.00

Procedure for Cream

1. In a stainless steel container, dissolve drug in caprylic/capric triglyceride while stirring.

2. In a separate stainless steel container melt cetyl alcohol, stearyl alcohol, span 60, mineral oil, arlacel 165, tween 60 and BHA at 70 -75°C.

3. Add the drug solution from Step 1 to the oily solution from Step 2 while mixing.

4. In an appropriate container heat water, sorbitol solution, edetate disodium, sorbic acid and potassium sorbate to 70-75°C.

5. Add the solution from Step 3 to the solution from Step 4 while emulsifying with a high speed mixer.

6. Cool the emulsion from Step 5 to room temperature until congels.

Example 2

Gel

Ingredients	% w/w
Compound A	0.00001 - 0.10
Butylated Hydroxyanisole (BHA)	0.02
Hydroxypropyl Cellulose	3.00
Ethyl Alcohol, USP	45.00
Water q.s. to	100.00

Procedure for Gel

1. In a stainless steel container dissolve BHA in ethyl alcohol and water mixture.

2. Dissolve drug in the solution from Step 1.

3. Disperse hydroxypropyl cellulose in the solution from Step 2.

Example 3

Ingredients	% w/w
Compound A	0.00001 - 0.10
Propylene Glycol	10.00
Caprylic/Capric Triglyceride	30.00
Butylated Hydroxyanisole (BHA)	0.02
Ethyl Alcohol, Absolute q.s. to	100.00

Procedure for Topical Solution

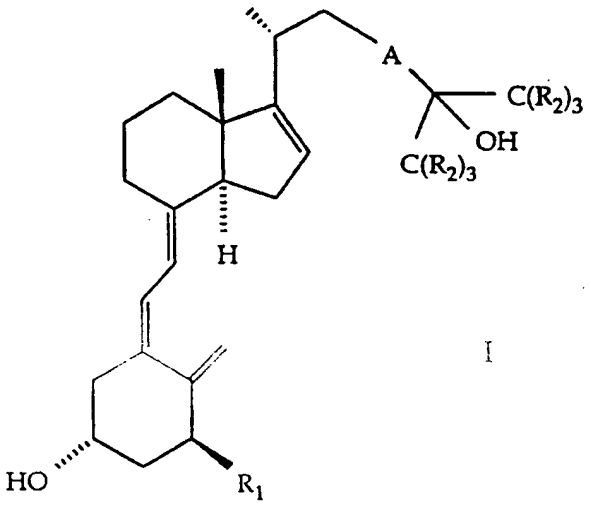
1. In a stainless steel container dissolve drug in ethyl alcohol.

2. Add and dissolve BHA to the solution from Step 1.

3. Add propylene glycol and caprylic/capric triglyceride to the solution from Step 2 and mix until solution becomes clear.

Claims

1. Composition for topically treating conditions associated with photodamaged skin containing a compound of the formula



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wherein R_1 is hydrogen, hydroxy or fluorine, R_2 is hydrogen or halogen and A is $-C\equiv C-$, $-C=C-$ or $-CH_2-CH_2-$, provided that when A is $-CH_2-CH_2-$, R_2 is hydrogen.

2. A composition according to claim 1, wherein in the compound of formula I, A is $-C\equiv C-$ or $-C=C-$.

3. A composition according to claim 1 or claim 2, wherein in the compound of formula I, R_1 is hydrogen or fluorine.

4. A composition according to any one of claims 1-3, wherein in the compound of formula I, R_2 is fluorine.

5. A composition according to claim 1, wherein in the compound of formula I, R_1 and R_2 are independently fluorine or hydrogen and A is $-C\equiv C-$ or $-C=C-$.

6. A composition according to claim 1, wherein the compound of formula I is 1α-fluoro-25-hydroxy-16-ene-23-yne-hexafluorochole-calciferol.

7. A composition according to claim 1, wherein the compound of formula I is 1α-fluoro,25-hydroxy-16,23E-diene-26,27-hexafluoro-cholecalciferol.

8. A composition according to claim 1, wherein the compound of formula I is 25-hydroxy-16,23E-diene-26,27-hexafluoro-cholecalciferol.

9. A composition according to any one of claim 1-8, containing at least .00001% by weight of said compound of formula I and an inert dermatologically acceptable carrier.

10. A composition according to claim 9, containing a compound of formula I in an amount of from about .00001% to about .1% by weight of the composition.

11. A composition according to claim 10, containing a compound of formula I in an amount of from about .0001% to about .01% by weight of the composition.

12. A composition according to claims 1-11, wherein said composition contains a cosmetically active ingredient.

13. A composition according to claim 12, wherein said cosmetically active ingredient is a sunscreen.

14. A composition according to any one of claims 1-13, wherein said composition is a gel, cream or ointment.

15. A composition according to any one of claims 1-13 for the treatment of wrinkling, elastosis or prematured aging of the skin.

16. The use of a compound of formula I as defined in claim 1 for the manufacture of a composition for the topical treatment of conditions associated with sundamaged skin.

17. The use according to claim 16 wherein said condition is wrinkling, elastosis or premature aging of the skin.

18. The novel compositions and use substantially as described hereinbefore.

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INTERNATIONAL SEARCH REPORT

Inte. ..tional Application No
PCT/EP 96/05805

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/59

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 087 619 A (BAGGIOLINI ET AL.) 11 February 1992 cited in the application see column 1, line 15 - column 2, line 55 see column 11, line 40 - line 54 see column 21, line 58 - column 22, line 27	1-3,5,9, 10, 14-16,18
Y	---	1-18
X	US 5 428 029 A (DORAN ET AL.) 27 June 1995 cited in the application see column 2, line 37 - line 41 see column 2, line 4 - line 11 see column 9, line 60 - column 10, line 49 see column 15, line 13 - line 50	1-5, 7-11, 14-16,18
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 5 451 574 A (BAGGIOLINI ET AL.) 19 September 1995 cited in the application see column 1, line 40 - column 2, line 25 see column 7, line 53 - column 8, line 28 see column 12, line 31 - line 68	1-6, 9-11, 14-16,18
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